

R E M A R K S

Claims 34, 37-39 and 45 are pending and stand rejected. The specific issues raised in the office action are addressed as follows. .

Claims 34, 37-39 and 45, are rejected under 35 U.S.C. § 103(a) as being unpatentable over Trau et al., U.S Patent No. 2003/0124564, published on July 3, 2003, in view of Li et al., U.S. Patent No. 5,168,104, issued on December 1, 1992, and Nakano et al., U.S. Patent No. 6,778,272, issued on August 17, 2004.

The current rejection is based upon a clear misinterpretation of Trau and fails to consider the specific fabrication methods in Trau or the manner that Trau achieves variation in coding. Trau's particle synthesis method simply does not permit formation of multiple porosity layers in any fashion, and certainly does not admit of the control over porosity that is presumed to have been obvious in the proposed modifications of Trau. The incorrect understanding of Trau's structure, fabrication method, and methods for achieving variance in optical signals from particles leads to flawed an incorrect conclusion of obviousness. There is no reasonable expectation of success or any other rational basis to conclude that Trau's particles could be modified to have multiple porosity interfaces and layers as required by the claims.

The office action interprets six words in paragraph 0091 "the varying porosity within each particle" in a manner that is contrary to Trau's teachings to reach a conclusion that "thin films contribute to the porosity variation." Pages 3 and 4. Later it is presumed that it would have been obvious and there is a reasonable expectation of success to control particle properties" and that producing a "library of particles is well known". P.5, citing Li and Nakano.

A first big problem in these conclusions is that there is no showing of how any porosity interfaces or layers could be produced by Trau's particle. This is why Trau, and any artisan reading Trau, would instead resort to the various Tags and coatings of Trau to achieve differentiation between particles. There is also no showing of how to produce a complex

optical signal from Trau based upon the porosity. The shell in Trau has nothing at all to do with the porosity in the structure that it covers. More importantly, the porous structure that is covered by the shell is not disclosed as having multiple porosity interfaces. Finally, there is no teaching that Trau's particles could be modified to have multiple porosity interfaces because the fabrication methods in Trau do not have control that is sufficient to produce multiple layers and multiple porosity interfaces.

The basic process in Trau is a modification of the Stöber process, that involves formation of polymer chains in a two reaction step process. The "polymer precipitates out of solution as nano-sized silica particles, which are colloiddally unstable. Consequently, the particles aggregate to form larger particles." [0011]. This process is modified by Trau to produce larger and more porous particles, but remains a colloidal polymer reaction that is not controllable in the manner presumed in the office action.

Trau's Synthesis Offers No Opportunity to Produce Porosity Interfaces and Layers

Trau uses a chemical synthesis method, namely Acid Catalyzed Processes, namely the "TEOS and the Stober Process". [0060]. Trau discloses procedures that form a hydrolysed silane emulsion and then add a cross-linker catalyst: "Organosilica particles are formed according to embodiments of the invention by a two step procedure. The first step is formation of an emulsion from mixing (a) acid, (b) water, and (c) a silane derivative to form a hydrolysed silane emulsion. The second step is to add a cross-linker catalyst to the emulsion to cross-link the silane derivative under controlled conditions to make particles of a desirable size." [0064].

The process of Trau can control the size of particles, via control of the level of agitation during synthesis that occurs after addition of the catalyst. More agitation produces smaller particles than less agitation:

[0075] Preferably the catalyst is added while the emulsion is stirred or agitated. When synthesizing large particles, the agitation is kept to a minimum. For making small particles, particularly less than 5 microns in diameter, greater agitation is needed. For a given solution condition and temperature, the exact amount of agitation needed for a given size of particle can be determined by one skilled in the art. In one embodiment, a minimum amount of vigorous stirring is used for smaller particles. The term "vigorous stirring" in this context means increasing molecular diffusion by at least the same amount as that experienced within 300 ml of water solution in a standard 500 ml flask at 1000 rpm while stirring with a regular 1 inch long teflon coated magnet (available from Nalgene Corp. U.S.A.).

Another method of controlling particle size involves chemical reaction control with viscosity: "the formed particle size is controlled to a larger dimension by use of a non-reactive viscosity enhancer that is dissolved in the water or water co-solvent solution." [0076]. Other ways to affect viscosity and particle size include a "water miscible solvent" and the injection of the silane emulsion into the catalyst solution. [0076].

The described process of Trau offers no opportunity to produce multiple layers having different porosities and interfaces between layers. The processes in Trau are largely unpredictable, and Trau discusses only "surprising" results for achieving particles of particular sizes without ever stating, suggesting or implying that a particle could be created having distinct interfaces and layers. Trau admits a lack of control and lack of understanding of the formation process, and no artisan would conclude that there is any control offered or possible to achieve multiple porosity interfaces:

[0060] While studying acid catalyzed hydrolysis of TEOS and the Stober process, the inventors made several observations and discoveries for altering particle morphology in a desirable way. First, the inventors found that incorporating APS into the reaction mixture increased particle size compared to the use of pure TEOS to form particles. However, instead of acquiring a homogenous shape, the particles made of APS presented a complex internal structure and exhibited poor yield.

[0061] In response to this result, the inventors hypothesized that protonation of the amine made the monomer and any subsequent polymer more soluble, and that polymerization of the APS would occur separately from polymerization of TEOS. Silane monomers which were less water soluble than APS then were investigated. These studies revealed that MPS is a useful monomer that can form the desired particles. Based on this insight, the inventors tried increasing the concentration of MPS and discovered that optimal size and yield could be obtained when 100% of the MPS coupling agent was used. However only droplets in an emulsion formed. The inventors then used a TEOS cross-linking catalyst such as NaF to form stable particles by cross-linking the droplets. The inventors further surprisingly discovered that they could improve particle size greatly by removing the surfactant typically present in the reaction mixture. The inventors also discovered that reducing the solution pH provided higher yield of particles.

The colloidal sequencing provides “high interior” surface area, as stated in [0062]. The exact mechanism for how the sequencing proceeds is not well understood, as stated in paragraph [0071]:

[0071] Most preferably, the emulsion lacks an added surfactant, as it was discovered that omitting a surfactant led to increased particle size. Without wishing to be bound by any one theory of this embodiment of the invention, we believe that when surfactant is present, the surfactant adsorbs to the surface of the droplets and forms a monolayer between the silica and aqueous bulk of the reaction mixture. When a cross-linking catalyst is added to the emulsion, the surfactant interferes with the catalyst reaching the silica in the droplet. Thus, surfactant may be added to control the particle size.

Trau claims to increase porosity and particle size over prior Stöber processes, but there is no description, reasonable expectation of success or even the slightest hint of any

method by which multiple porosity interfaces, layers of different optical thicknesses, or multiple layers could be produced in a particle produced by the colloid formation processes.

The “varying porosity” in Trau is clearly a random variation of pore and channel size that results from the not very well understood or not very predictable process of Trau. Trau’s particles include a range of pore sizes that are linked by channels, but there is no disclosure of interfaces, layers, or the ability to control where the pores and channels form “Desirably, the particles contain pores between approximately 0.1 and 5 microns in mean diameter, wherein at least two of the pores are linked by channels less than 75 nanometers in mean diameter.” [0019]. “The term ‘porous’ refers to a structure having pores between approximately 0.1 and 5 microns in mean diameter, wherein the pores may be linked by small channels less than about 200 nm, preferably less than 100 nm, and more preferably about 75 nm in diameter.” [0036].

In sum, even if there were recognition of the desirability of producing multiple pore layers with multiple porosity interfaces, there is no suggestion of how such porosity control could be achieved in the context of Trau’s colloid fabrication method. The random structure of pores and channels is clearly shown in the drawings, and the interpretation that “varying pore size” is anything other than random is contradicted by the images of sample particles.

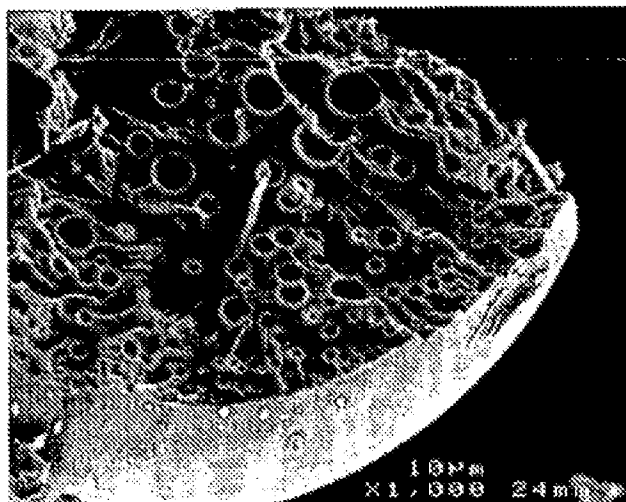


FIG. 5A

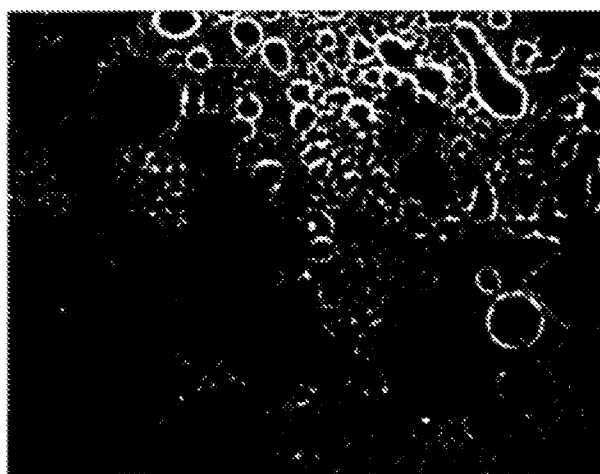


FIG. 7

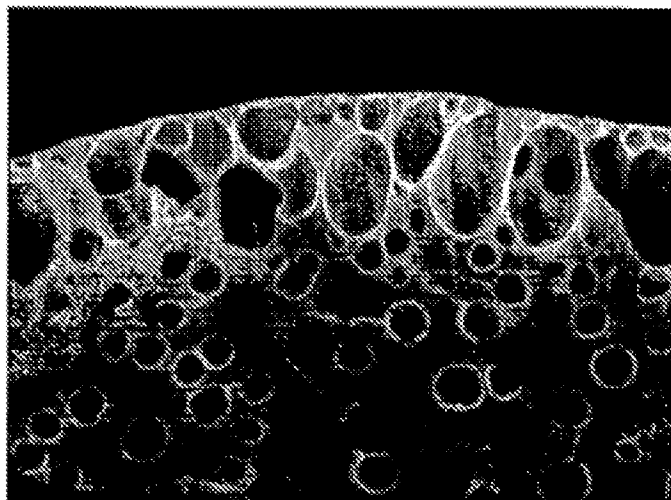


FIG. 10B

Trau's Clear Silicon Shells Don't Affect Porosity

Page 3 of the office action links that silica shell of Trau to the porosity, and states that "thin films that contribute to the porosity variation and allow for the coding." This conclusion is unfounded and unsupported. The shell is not part of the two step formation process that forms the pores, and is not involved in the reactions that produce particles. The clear silica shells are clearly described as being formed after the porous particles are formed. "In a related embodiment, the particle's pores are filled with a fluid, optionally after adding a visual tag such as a fluorogenic molecule, subsequently rinsed, and then the pore openings treated with a cross-linker to prevent efflux of fluid from the pores. In a preferred embodiment, a fluorescent marker is covalently attached to the interior surface of the particle or added non-covalently in a fluid, and the pores are sealed by coating with a silicon shell." [0085].

The Office Action Associates Unrelated Properties of Porosity and Shell Thickness

Page 5 of the office action attempts to combine different portions of Trau's particle and coating in a manner that implies that there is a porous layer of different thickness. Page 5 states "Trau also teaches refractive index changes and varying porosity

and varying thickness.” This improperly suggests that Trau has a high level of control of porosity, but Trau instead resorts to other optical controls, namely the filling of the pores with a substance having a known density, tagging the particles, or having different thickness clear silicon shells. None of these methods affect the porosity of the particles, because all of the methods are applied after the particles are formed.

One of Trau’s mechanism of controlling optical response with the porous part of the particle has to do with density, i.e., the pores are filled to a particular density or with a substance. “The high pore volume allows addition of a solvent or other substance of known density to the particles such that, after entering the pores, the particle density is adjusted. The density is set by incubating the particles in a given fluid, such as ethanol, methanol, propylene glycol, mercury, glycerol, and the like.” [0083].

Another of Trau’s mechanisms of controlling optical response uses fluorescence tags. “Advantageously, an optical tag is added to the particles prior to coating with a silica shell. In an embodiment thereof, the optical tag is a fluor or phosphor.” This, like the density control is accomplished after formation of the particles via the chemical process.

The third of Trau’s mechanisms of controlling optical response is the clear silica shell, which is formed after the particle formation. This shell is used with the small particles that are formed by a prior art Stöber process, as described in [0088]. “In another embodiment of the invention, a particle prepared by the Stober process is coated with a clear silica layer. In this case preferably a small particle between 0.02 and 3 microns and more preferably between 0.1 and 1 micron in diameter is prepared by the Stober process.” As noted early in Trau, the Stöber process has limits as to porosity and size. [0013].

Trau’s Coding is Fundamentally Different than that Claimed

Page 5 of the office action concludes that “Trau teaches the preparation of a library of particles meeting the instant invention, he does not explicitly state that the binders are located within the pores of the particles, or teach that the library of particles were

prepared from a library of codes via a computer waveform controlled etch.” As shown above, to the extent that Trau produces any “library” it will be based upon different density (because of pores being filled), different tags applied (such as phosphor), or by different thicknesses of clear silica shell. There is no possible library based upon any “etching” because Trau forms particles by polymer synthesis. That process is clearly demonstrated to be unpredictable by Trau, which characterizes changes in particle sizes as a result of omitting surfactants as “surprising”. [0061]. No artisan would believe that a computer could aid or control the polymerization process to form libraries based upon differing porosities between particles in Trau, and there is certainly no basis to conclude that a polymerization process as in Trau could be modified to produce multiple porosity interfaces or multiple layers. Particles of the invention can produce complex codes, that can be resolved from a signal particles. Such coding is not available from Trau, which is precisely why Trau relies upon other mechanisms of filling pores, adding tags, and adding coatings.

Trau’s Coding Could not Be Modified by Nakano’s Plasma Chamber Processing Method

The Examiner relies upon Nakano for allegedly suggesting computer controlled modification of Trau’s polymerization process but there is no opportunity for such control Nakano processes. Nakano concerns plasma processing and measurement of particles suspended in a plasma processing chamber. The idea that plasma processing has any application to Trau is far-fetched, and no artisan would consider processes related to a plasma chamber as even marginally relevant to Trau’s polymerization processes.

The Coding Could not Be Modified by Nakano’s Wafer Processing Method

The integral coding in the multiple layer film by interfaces and thicknesses has important advantages over Trau’s polymerization processes. The claimed multiple optical thicknesses that are part of the physical porosity structure and porosity interfaces can produce complex codes without resort to pore filling, tags, and optical coatings. As stated on page 8 of the instant application, “A preferred embodiment is a particle 10 having multi-layer films 121-12N that have mismatched optical thicknesses. Optical thickness is defined as the

refractive index of a layer multiplied by its metric thickness.” The particles of the invention can perform analyte detection and the use of receptors within the pores. The claimed particles and invention enable a “code or group of codes...[to] reproduce the same optical signature over and over again, permitting the manufacture of films having the same codes. In addition, different codes may be selected from the library of codes to produce films having different optical signatures.” P7, L6-10. Because the porous codes are an integral and orderly part of the porous structure, it is not possible for part of the code to be lost, scrambled or photobleached. The layered porous-silicon encoded structures offer several advantages over existing encoding methodologies. Porous-silicon encoded structures can be constructed that display features spanning the visible, near-infrared and infrared regions of the spectrum. With the invention claimed, compared to other coding techniques (including Trau’s use of clear silicon coatings on particles to provide different sized particles) provides a more powerful and accurate coding scheme. Encoded films can be assayed using a conventional fluorescence tagging technique, and sensitive chemical and biochemical detection can also be built into the optical structure of the encoded films, which is not possible with Trau’s particles that are sealed with a clear film or filled with other materials.

Claims 34, 37-42 and 45, are rejected under 35 U.S.C. 103(a) as being unpatentable over Trau, Li and Nakano, as applied to claims 34,37-39 and 45 above, and further in view of Chan et al., U.S Patent No. 7,226,733, issued on June 5, 2007, in view of Ghadhiri et al., U.S. Patent No. 6,248,530, issued on June 19, 2001. The rejection is traversed.

This rejection relies upon the Trau/Li/Nakano theories discussed above. The above is believed a sufficient traversal. Previous comments regarding Chan and Ghadhiri being combined with Trau are also maintained, but will not be repeated.

For all of the above reasons, applicants request reconsideration and allowance of the application. Should the examiner believe that outstanding issues exist or that a

conference would expedite prosecution, the examiner is invited to contact the undersigned attorney at the below listed number.

Respectfully submitted,

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